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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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PATRICK M. DWYER
PROTEOTECH, INC.
SUITE 114
1818 WESTLAKE AVENUE
SEATTLE, WA 98109

| EXAMINER |
|---|
| CHERNYSHEV, OLGA N |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | 12 |

DATE MAILED: 04/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/938,275 | CASTILLO ET AL. | |
| | Examiner | Art Unit | |
| | Olga N. Chernyshev | 1646 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *6-10,13,14 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,11,12,15,17 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of species of SEQ ID NO: 3 in Paper No. 8 is acknowledged. Claims that encompass elected species are 1-5, 11, 12, 15, 17 and 18. Please note that claim 15 and not claim 14, as identified by Applicant, is directed to the elected species.

Claims 6-10, 13, 14 and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claims 1-5, 11, 12, 15, 17 and 18, in so far as they encompass a polypeptide of SEQ ID NO: 3, are under examination in the instant office action.

### *Drawings*

2. Figure 9 of the instant application is presented on separate pages or in separate panels. 37 C.F.R. § 1.84(u) (1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. For example, the two panels of Figure 9 in the instant specification should be renumbered "Figure 9A" and "Figure 9B" rather than "Figure 9". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(u) (1), the specification should be amended to change the Brief Description of the Drawings and the rest of the specification to refer to each Figure accordingly. If, for example, Figure 9 is divided into Figures 9A-9B, then the Brief Description and all the references to this figure in the specification must refer to this Figure in the same manner.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-5, 11, 12, 15, 17 and 18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-5, 11, 12, 15, 17 and 18 are directed to a method for treating beta-amyloid protein formation in a beta-amyloid protein disease by administration of a polypeptide having a conformational similarity to a fragment of a laminin protein. The instant specification describes results of the *in vitro* experiments establishing the ability of laminin or specific fragments thereof to inhibit formation of amyloid fibrils. The specification teaches that such inhibitory ability of laminin or its fragments is amyloid-specific because the inhibitory effects of laminin did not occur with amylin fibril formation. Based on the "demonstrated specificity of the observed laminin inhibitory effects on Alzheimer's disease amyloid" (page 36, lines 16-17 of the instant specification), it is asserted that laminin or its fragments if administered to a patient suffering from a beta-amyloid protein disease would also inhibit formation and deposition of amyloid fibrils. However, the instant specification fails to describe how to practice the claimed method, thereby requiring undue experimentation for a skilled practitioner to discover how to make and use Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention is the demonstration that laminin or fragments thereof are capable to inhibit amyloid protein formation in vitro. Amyloid protein is a major component of amyloid plaques, which are the hallmark of Alzheimer's disease. Art clearly recognizes that inhibition of amyloid fibril formation can be achieved *in vitro* by alteration of pH level, for example, or by addition of number of different factors, like laminin (Bronfman et al., 1996, Neurosci. Lett. 218, pp. 201-203) or α-1-antichymotrypsin (Aksenova et al., 1996, Neurosci. Lett., 211, pp.45-48), for example. However, it is not recognized in the art that inhibitory effect of laminin on amyloid fibril formation that has been shown to take place *in vitro* would also be effective *in vivo*.

Thus, the state of the art can be characterized as (1) recognizing that laminin, as well as other factors, can inhibit formation of amyloid fibrils *in vitro*, and (2) that the observation of binding and inhibition *in vitro* is not apparently predictive of the therapeutical effectiveness *in vivo*. There is no information available in the art at the time the invention was made that would indicate that any of the factors that can inhibit amyloid formation *in vitro* can also have the similar effect *in vivo* when administered to a patient. In view of the absence of such information

found in the prior art, one skilled in the art would have to relate only to the instant disclosure in order to practice the claimed invention.

To practice such a method would require knowledge of the route, duration and quantity of administration of that protein to a subject and this information is not provided by the instant specification. The mere list of prophetic doses and regimes exemplified on pages 63-65 of the instant specification clearly fails to satisfy a routine practitioner. The instant specification has also failed to disclose how these parameters are to be determined, how a similar method was practiced in the art with a different agent or to provide even a single working example, prophetic or actual, of the claimed method practiced using, for example, an art recognized animal model. In the absence of this guidance a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of a polypeptide having a conformational similarity to a fragment of a laminin protein of the instant invention and in determining a suitable route of administration. The instant situation is directly analogous to that which was addressed in *In re Colianni*, 195 U.S.P.Q. 150,(CCPA 1977), which held that a "[d]isclosure that calls for application of "sufficient" ultrasonic energy to practice claimed method of fusing bones but does not disclose what "sufficient" dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequency, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. 112 first paragraph".

Furthermore, the instant specification fails to teach how to determine "conformational similarity to a fragment of a laminin protein" in general and the level of 70% or 90% of similarity in particular. It appears that binding of a polypeptide having such similarity to laminin

to an amyloid protein is crucial for practicing the instant invention. Without knowledge on how to make or choose a polypeptide that is conformationally similar to a fragment of a laminin protein, one skilled in the art would be forced into undue experimentation to practice the claimed method.

Applicant's invention is predicated on the finding that laminin or fragments thereof are capable of inhibition of amyloid fibril formation *in vitro*. Applicant further extrapolates this result into a method for treating beta-amyloid protein formation, deposition or accumulation in a beta-amyloid protein disease by administration of a polypeptide having a conformational similarity to a fragment of laminin, thus, asserting a therapeutic benefit of such treatment. Accordingly, it would appear that Applicant provides a single finding, and then presents an invitation to experiment to determine if the effect found *in vitro* would also be effective *in vivo*.

The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. In view of the lack of teachings and unpredictability of the art set forth earlier, and also the absence of the working examples, the instant specification is not found to be enabling for a method for treating beta-amyloid protein formation, deposition or accumulation in a beta-amyloid protein disease by administration of a polypeptide having a conformational similarity to a fragment of laminin. It would require undue experimentation and making a substantial inventive contribution for the skilled artisan to discover how to use Applicants' invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-5, 11, 12, 15, 17 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step that leads to the treatment of beta-amyloid formation, deposition or accumulation.

6. Claim 1 is also vague and ambiguous for recitation of "treating beta-amyloid formation, deposition or accumulation". It is not obvious what act of treatment is intended by the claim.

7. Claims 1-4 are vague and ambiguous for recitation "conformational similarity". The metes and bounds of the recitation cannot be determined form the claims or the instant specification.

8. Claims 1, 15, 17 and 18 are vague and indefinite for recitation of "therapeutically effective amount". It is not clear and cannot be determined from the claim what is the amount of a polypeptide is effective for and what therapeutic effect is achieved. Clarification is required.

9. Claim 12 recites the limitation "globular repeats" in claim 11. There is insufficient antecedent basis for this limitation in the claim.

10. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step that leads to the treatment of a patient.

11. Claim 15 is further indefinite and ambiguous for recitation "to interfere with beta-amyloid protein formation". Term "to interfere" is a relative term and encompasses increase as

well as decrease in protein formation. Therefore, it is not clear and cannot be determined what interference is intended by the claim.

12. Claims 5 and 11 are indefinite for being dependent form indefinite claims.

***Conclusion***

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D. ONC
April 18, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600